Dietary antioxidants and risk of myocardial infarction in the elderly: the Rotterdam Study[1–3]

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ABSTRACT

Background: Epidemiologic studies have shown dietary antioxidants to be inversely correlated with ischemic heart disease.

Objective: We investigated whether dietary β-carotene, vitamin C, and vitamin E were related to the risk of myocardial infarction (MI) in an elderly population.

Design: The study sample consisted of 4802 participants of the Rotterdam Study aged 55–95 y who were free of MI at baseline and for whom dietary data assessed by a semiquantitative food frequency questionnaire were available. During a 4-y follow-up period, 124 subjects had an MI. The association between energy-adjusted β-carotene, vitamin C, and vitamin E intakes and risk of MI was examined by multivariate logistic regression.

Results: Risk of MI for the highest compared with the lowest tertile of β-carotene intake was 0.55 (95% CI: 0.34, 0.83; *P* for trend = 0.013), adjusted for age, sex, body mass index, pack-years, income, education, alcohol intake, energy-adjusted intakes of vitamin C and E, and use of antioxidative vitamin supplements. When β-carotene intakes from supplements were considered, the inverse relation with risk of MI was slightly more pronounced. Stratification by smoking status indicated that the association was most evident in current and former smokers. No association with risk of MI was observed for dietary vitamin C and vitamin E.

Conclusion: The results of this observational study in the elderly population of the Rotterdam Study support the hypothesis that high dietary β-carotene intakes may protect against cardiovascular disease. We did not observe an association between vitamin C or vitamin E and MI. *Am J Clin Nutr* 1999;69:261–6.

KEY WORDS Myocardial infarction, ischemic heart disease, dietary antioxidants, β-carotene, vitamin C, vitamin E, vitamin supplements, elderly, the Rotterdam Study, Netherlands

INTRODUCTION

Several epidemiologic studies have shown dietary antioxidants to be inversely associated with ischemic heart disease (1–9). The antioxidants β-carotene, tocopherol, and vitamin C have been implicated in preventing or slowing down the atherosclerotic process by inhibiting LDL oxidation. The most consistent and reliable association has been seen with vitamin E, either with supplementation or with relatively high dietary intakes. β-Carotene and vitamin C intakes have been less clearly associated with a reduced risk of ischemic heart disease (10). Most epidemiologic studies of dietary antioxidants and risk of ischemic heart disease have focused on middle-aged populations. In the present study we investigated whether dietary intakes of the antioxidants β-carotene, vitamin C, and vitamin E are related to the risk of myocardial infarction (MI) in an elderly population.

SUBJECTS AND METHODS

Study population

The Rotterdam Study is a community-based, prospective cohort study of 7983 persons (response rate 78%) aged ≥55 y living in Ommoord, an urban district in Rotterdam, Netherlands. The aim of the study is to investigate the incidence of and the risk factors for chronic and disabling cardiovascular, neurodegenerative, locomotor, and ophthalmic diseases, as described elsewhere (11). The study was approved by the Medical Ethics Committee of Erasmus University, and written, informed consent was obtained from all participants. Follow-up for ischemic heart disease mortality started after the baseline survey in 1990 and follow-up information was available for 94% of the cohort until April 1996. Of the 5159 subjects with dietary data, 173 subjects had an MI during the follow-up period. Because of possible changes in dietary patterns, subjects with a previously known MI at baseline (n = 357) were excluded from the analysis. Thus, 4802 subjects made up the current analysis. During an average follow-up time of 4 y, 124 cases of first fatal or nonfatal MI occurred.

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Case ascertainment

The duration of the follow-up period, starting at the baseline examination and lasting until April 1996 for the present analysis, was 3–7 y ($\bar{x}$: 4 y). The vital status (eg, change of address or death) of participants' information was obtained at regular intervals from the municipal health service in Rotterdam. Information on fatal and nonfatal endpoints for 85% of the cohort was obtained from the general practitioners (GPs) in the study district of Ommoord, who regularly report such information to the data center of the Rotterdam Study. All possible myocardial infarctions by the GPs were verified by research physicians from the Rotterdam Study by analyzing the records of the participating practitioners and medical specialists. In April 1996, the medical records of the 15% of the cohort with GPs from outside the Ommoord area were checked by research physicians; additional information was collected for all possible myocardial infarctions. In the case of death, causes and circumstances were determined by examining hospital-discharge records and by questioning the GPs. Follow-up information was available for 94% of the cohort.

Classification of fatal and nonfatal events was based on the International Classification of Diseases (ICD) (12). Cases of first nonfatal or fatal MIs (ICD-10:I21-I24) were selected and classified independently by 2 research physicians. If there was disagreement, a consensus was reached in a special session. All events were verified by a medical expert in the field of cardiovascular disease, whose judgment was considered final.

Measurements

Baseline information on current health status, medical history, drug use, education level, income, and smoking behavior was obtained with a computerized semiquantitative food-frequency questionnaire (SFFQ) during a home interview. Height and weight were measured and body mass index [BMI; wt (in kg)/ht^2(in m)] was calculated as a measure of obesity. Sitting blood pressure (BP) was measured in the right upper arm with a random-zero sphygmomanometer; the average of 2 measurements was used. Subjects were considered to be hypertensive if they had a systolic BP ≥140 mm Hg, had a diastolic BP ≥90 mm Hg, or used antihypertensive drugs. A venipuncture was performed and serum total and HDL-cholesterol concentrations were determined with an automated enzymatic procedure. Subjects were classified as hypercholesterolemic if their serum cholesterol concentrations were ≥6.5 mmol/L.

Dietary assessment

The SFFQ completed at baseline aimed to assess habitual food intakes during the past year and included 170 food items in 13 food groups and questions about dietary habits, supplementation, and prescribed diets. The dietary assessment consisted of a simple self-administered questionnaire that was completed at home (completion time: ≈20 min) and a subsequent structured interview with a trained dietitian (time allocated: ≈20 min). The structured interview was based on the contents of the completed questionnaire and was conducted during the subjects' second visit to the study center. The SFFQ data were converted to nutrient intakes by using the computerized Dutch Food Composition Table (13). Data for β-carotene, retinol, and tocopherol were updated by using an additional database of the Netherlands Institute of Public Health and Environmental Protection (YCJ Vollebregt and EJM Feskens, unpublished observations, 1993). Nutritional supplement intakes were not considered because dose and duration were not recorded with sufficient accuracy.

The validity of the SFFQ was assessed in a subsample of 80 men and women aged 55–75 y. Nutrient intakes estimated from the SFFQ were compared with estimated nutrient intakes from food records completed on 15 d and collected over 1 y (14). The ability of the SFFQ to rank subjects adequately according to their dietary intakes was demonstrated by Pearson's correlation coefficients of 0.4–0.8 adjusted for sex, age, total energy intake (15), and within-person variability in daily intakes (16), and a high degree of classification into the same or an adjacent quintile (76.8% for energy-adjusted data).

Data analysis

All analyses were performed for men and women combined. Energy-adjusted nutrient intakes were derived by adding the median nutrient intake to the residuals from regression analysis of nutrients on energy intake (15). The association between energy-adjusted antioxidants and risk of MI was examined primarily by multivariate logistic regression. Because vitamins can be ingested from both foods and supplements, exposure to each vitamin was studied in 2 ways.

First, dietary antioxidant intakes from food sources were categorized into tertiles and the risk of MI in the highest and middle tertiles was compared with the risk of MI in the lowest tertile. The initial analysis examined associations adjusted for age and sex. Furthermore, the analyses were adjusted for BMI, pack-years (average number of packs of cigarettes smoked times the number of years smoked), equivalent household income (5 categories), highest education attained (5 categories), and alcohol intake (5 categories). Supplement preparations containing β-carotene, vitamin C, or vitamin E were combined and added to the model as a separate variable. This allowed investigation of the relation between dietary antioxidants and the risk of MI unconfounded by supplemental antioxidant vitamin intake.

Second, to simultaneously study the effects of antioxidants from food sources and supplement preparations, users of β-carotene, vitamin C, vitamin E, or multivitamin supplements were categorized into the highest tertile of the correspondent dietary intake. The age- and sex-adjusted risk of MI according to tertile of intake was investigated and the models were subsequently adjusted for the above-mentioned factors, except for supplemental antioxidant intakes. The associations between tertiles of energy-adjusted β-carotene, vitamin E, and vitamin C with risk of MI were expressed as odds ratios with 95% CIs. Results were considered significantly different at the two-sided 0.05 α level. Statistical analysis was performed by using SAS software (release 6.11; SAS Institute, Cary, NC).

RESULTS

The mean (±SD) age of the 1856 men and 2946 women was 67.0 ± 7.3 and 67.9 ± 8.0 y, respectively. Compared with the general population of the Rotterdam Study for whom dietary data were available (n = 5434), the study population for the present analysis did not differ significantly in characteristics such as age, BMI, blood pressure, income, education level, or nutrient intake. Vitamin supplements containing either β-carotene, vitamin C, or vitamin E were used by 11.8% of the study population.

Details of the association between intakes of energy-adjusted antioxidants and selected baseline characteristics are presented in **Table 1**. Because sex and age were not equally distributed across tertiles of dietary antioxidant intake, age and sex were adjusted for. Mean energy-adjusted dietary intakes of β-carotene were 0.84 mg/d in the lowest and 2.11 mg/d in the highest tertile, of vitamin C were 63 mg/d in the lowest tertile and 170 mg/d in the highest

TABLE 1
Baseline characteristics by tertile of energy-adjusted dietary β-carotene, vitamin E, and vitamin C intakes[1]

	Energy-adjusted dietary β-carotene				Energy-adjusted dietary vitamin E				Energy-adjusted dietary vitamin C			
	1 (lowest) <1.13 mg/d (*n* = 1601)	2 1.13–1.57 mg/d (*n* = 1601)	3 (highest) >1.57 mg/d (*n* = 1600)	*P* for trend	1 (lowest) <10.2 mg/d (*n* = 1601)	2 10.2–14.2 mg/d (*n* = 1601)	3 (highest) >14.2 mg/d (*n* = 1600)	*P* for trend	1 (lowest) <87 mg/d (*n* = 1601)	2 87–126 mg/d (*n* = 1601)	3 (highest) >126 mg/d (*n* = 1600)	*P* for trend
BMI (kg/m^2)	26.0	26.4	26.3	0.011	26.3	26.3	26.1	0.323	26.0	26.2	26.5	0.003
Current smokers (%)	29.1	25.9	19.5	0.015	27.6	25.4	21.7	0.007	31.4	22.8	20.0	0.001
Hypertension (%)[2]	48.4	48.3	49.0	0.610	48.6	48.5	48.6	0.330	47.3	49.9	48.5	0.381
Hypercholesteremia (%)[3]	52.5	48.0	49.0	0.063	51.3	48.8	49.5	0.212	52.0	49.9	47.5	0.786
Diabetes (%)	9.5	9.3	9.0	0.631	8.0	9.8	9.7	0.170	10.2	9.6	7.9	0.052
Alcohol intake (mg/d)	12.1	10.9	10.9	0.021	14.1	10.5	9.7	<0.001	12.0	11.6	10.3	0.002
Antioxidative vitamin supplementation (%)[4]	11.0	11.5	11.3	0.651	10.3	11.9	11.5	0.577	11.6	10.9	11.3	0.482
Energy-adjusted vitamin C intake (mg/d)	93.8	108.7	132.8	<0.001	1.27	1.45	1.59	<0.001	1.19	1.44	1.71	<0.001
Energy-adjusted vitamin E intake (mg/d)	11.8	13.0	14.2	<0.001	104.6	112.3	118.6	<0.001	12.3	13.0	13.7	<0.001

[1] Adjusted for age and sex.
[2] Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication.
[3] A serum cholesterol concentration ≥6.5 mmol/L.
[4] Use of either β-carotene, vitamin E, vitamin C, or multivitamin supplements.

TABLE 2
Risk of myocardial infarction (MI) and 95% CIs according to energy-adjusted tertiles of dietary β-carotene, vitamin C, and vitamin E intakes

Variable	Tertiles of dietary energy-adjusted intake			*P* value for trend
	1 (lowest)[1] (*n* = 1601)	2 (*n* = 1601)	3 (highest) (*n* = 1600)	
β-carotene intake				
Number of MIs	53	41	30	
Energy-adjusted β-carotene intake (mg/d)	<1.13	1.13–1.57	>1.57	
Relative risk (95% CI)				
Age and sex adjusted	1.00	0.74 (0.48, 1.12)	0.55 (0.34, 0.86)	0.009
Multivariate adjusted 1[2]	1.00	0.74 (0.48, 1.12)	0.57 (0.36, 0.91)	0.017
Multivariate adjusted 2[3]	1.00	0.72 (0.47, 1.10)	0.55 (0.34, 0.83)	0.013
Vitamin E intake				
Number of MIs	33	49	42	
Energy-adjusted vitamin E intake (mg/d)	<10.2	10.2–14.2	>14.2	
Relative risk (95% CI)				
Age and sex adjusted	1.00	1.41 (0.90, 2.23)	1.05 (0.66, 1.69)	0.916
Multivariate adjusted 1[2]	1.00	1.40 (0.90, 2.22)	1.07 (0.67, 1.73)	0.836
Multivariate adjusted 2[3]	1.00	1.52 (0.97, 2.42)	1.21 (0.75, 1.98)	0.528
Vitamin C intake				
Number of MIs	47	41	36	
Energy-adjusted vitamin C intake (mg/d)	<87	87–126	>126	
Relative risk (95% CI)				
Age and sex adjusted	1.00	0.89 (0.58, 1.37)	0.84 (0.54, 1.30)	0.446
Multivariate adjusted1[2]	1.00	0.94 (0.58, 1.37)	0.88 (0.56, 1.38)	0.581
Multivariate adjusted 2[3]	1.00	1.01 (0.65, 1.56)	1.05 (0.65, 1.67)	0.856

[1] Reference category.
[2] Adjusted for age, sex, body mass index, pack-years, equivalent household income (5 categories), education (5 categories), and alcohol intake (5 categories).
[3] Adjusted for age, sex, body mass index, pack-years, equivalent household income (5 categories), education (5 categories), alcohol intake (5 categories), use of antioxidative vitamin supplements, and categories of energy-adjusted β-carotene, vitamin C, and vitamin E intakes.

tertile, and of vitamin E were 7.8 mg/d in the lowest tertile and 18.5 mg/d in the highest tertile. The percentage of hypercholesterolemic subjects was higher in the lowest tertile than in the upper 2 tertiles of β-carotene intake. The percentage of current smokers declined significantly across tertiles of β-carotene. A similar significant decline was observed for the percentage of current smokers across tertiles of vitamin C and vitamin E (Table 1). In addition, mean alcohol intake was highest for the lowest tertiles of dietary antioxidant intake. Although dietary antioxidant intake generally increased across tertiles of the other antioxidants, the increase in β-carotene and vitamin C with tertiles of vitamin E was modest. Spearman correlation coefficients were highest between β-carotene and vitamin C ($r = 0.36$, $P < 0.0001$) and lowest between vitamin C and vitamin E ($r = 0.12$, $P < 0.0001$).

β-Carotene from food sources was inversely related to risk of MI after adjustment for age and sex (**Table 2**). The relative risk for the highest compared with the lowest tertile was 0.55 (95% CI: 0.34, 0.86; *P* for trend = 0.009). After additional adjustment for BMI, pack-years, equivalent household income, education level, and alcohol intake, the observed association remained (Table 2). Further adjustment for vitamin E and vitamin C did not alter the observed association. To evaluate whether the observed association of β-carotene from food sources was independent of antioxidative vitamin supplementation, antioxidant vitamin supplement use (β-carotene, vitamin C, vitamin E, or multivitamins) was included in the multivariate model. The relative risk of MI for antioxidant vitamin supplement users compared with nonusers was 0.49 (95% CI: 0.21, 0.99; $P = 0.008$). The relative risk of the highest compared with the lowest tertile of β-carotene intake was 0.55 (95% CI: 0.34, 0.85; *P* for trend = 0.013). Further adjustment for dietary fats and cholesterol did not change the observed association. When β-carotene intakes from food sources and supplements were considered simultaneously, the age- and sex-adjusted relative risk was 0.49 (95% CI: 0.31, 0.86; *P* for trend = 0.019) for the highest compared with the lowest tertile of β-carotene consumption. Multivariate adjustment led to only slight changes in the point estimate (highest compared with lowest tertile: relative risk, 0.50; 95% CI: 0.31, 0.82; *P* for trend = 0.006).

The association between dietary β-carotene and the risk of MI differed significantly on the basis of baseline smoking status. We

TABLE 3
Tertiles of energy-adjusted dietary β-carotene intake and risk of myocardial infarction (95% CIs) according to smoking status[1]

Variable	Tertiles of energy-adjusted dietary β-carotene intake			*P* value for trend
	1 (lowest)[2] <1.13 mg/d	2 1.13–1.57 mg/d	3 (highest) >1.57 mg/d	
Current smokers (*n* = 1133)	1.00	0.87 (0.42, 1.83)	0.45 (0.17, 1.10)	0.058
Former smokers (*n* = 1984)	1.00	0.53 (0.27, 1.01)	0.32 (0.14, 0.66)	0.002
Nonsmokers (*n* = 1685)	1.00	1.00 (0.39, 2.55)	1.68 (0.65, 4.39)	0.299

[1] The multivariate-adjusted model was adjusted for age, sex, body mass index, pack-years, equivalent household income (5 categories), education (5 categories), alcohol intake (5 categories), categories of energy-adjusted vitamin C and vitamin E, and antioxidative vitamin supplementation.
[2] Reference category.

observed a significant inverse association between β-carotene intakes and risk of MI in former smokers and a nonsignificant inverse association among current smokers (**Table 3**). No interaction between β-carotene intakes and smoking status was observed. These associations were the same when β-carotene intakes from food and supplements were considered simultaneously. We did not observe an association between tertiles of dietary vitamin C intake and risk of MI in an age- and sex-adjusted model (Table 2). In addition, no association with risk of MI was observed for tertiles of vitamin E. Stratification by smoking status did not alter these results.

DISCUSSION

In the elderly cohort of the Rotterdam Study, we observed an inverse association of β-carotene intake with risk of MI, independent of antioxidative vitamin supplement use. The association observed was most evident in former and current smokers. Dietary vitamin C and vitamin E were not associated with risk of MI.

Before these results can be interpreted, some methodologic issues should be considered. Potential bias due to incomplete follow-up was unlikely to have occurred because the follow-up rate was high (94%). Ascertainment of cases was facilitated by the close cooperation with GPs in the study district of Ommoord and linkage to the municipal health service of Rotterdam. Because all events were classified independently by 2 research physicians and subsequently by a cardiovascular disease expert, inaccuracies in diagnosis coding were minimized. Because subjects with a previous diagnosis of MI may have altered their diet as a consequence of the disease, subjects reporting hospitalization for MI at baseline were excluded from the analysis.

Certain methodologic issues may have weakened the observed association between dietary antioxidant vitamin use and risk of MI. A serious limitation of studies addressing diet are inaccuracies in the determination of intakes. Random misclassification of dietary habits may decrease the ability to detect associations between diet and disease, as do changes in dietary habits during the follow-up period. The observed weak correlation between dietary vitamin intake and bioavailability may have further diluted the observed associations between dietary antioxidants and disease, eg, MI. Insufficient heterogeneity of dietary intake in the population may make it more difficult to detect diet-disease associations. In the present study, contrasts in the range of dietary intake between the lowest and the highest tertiles were modest for β-carotene, vitamin E, and vitamin C; ie, the between-person variation was low. In addition, β-carotene, vitamin E, and vitamin C supplements were only used by a small proportion of the population: 0.6% used β-carotene, 1.4% used vitamin E, and 5.7% used vitamin C. Inclusion of supplemental dietary intakes somewhat strengthened the association between β-carotene intake and risk of MI.

Observational studies have indicated that β-carotene may exert a protective effect against ischemic heart disease, although the evidence is not conclusive (10). Studies focusing on β-carotene in plasma or adipose tissue, however, yielded consistent results in general. Biologically plausible mechanisms such as the potential of antioxidants to scavenge free radicals (17) and the ability of antioxidants to inhibit lipid peroxidation (18, 19) support these findings, although the latter mechanism remains controversial (20, 21). In middle-aged populations, subjects with low plasma β-carotene concentrations were found to have an elevated risk of angina pectoris (1) and MI (22); however, MI appeared to be limited to smokers with low serum β-carotene concentrations. Risk of MI was also considerably elevated in current smokers with low β-carotene concentrations in adipose tissue (23). In contrast, there was an inverse association between total plasma carotenoid concentrations and risk of fatal ischemic heart disease and nonfatal MI in nonsmoking hyperlipidemic men (24). Studies focusing on the elderly showed either no association between carotenoid concentrations and dietary intake and the risk of ischemic heart disease (7) or an inverse association between intake of carotene-containing fruit and vegetables and the risk of cardiac death due to MI and ischemic heart disease (5). In the present study, we observed a significant protective effect of β-carotene intakes against the risk of MI in the elderly population of the Rotterdam Study, which was most evident in current and former smokers.

The effects of β-carotene in our study and other observational studies are at odds with recent findings from large supplement intervention trials of chronic disease prevention (25–29). These trials reported either no effect of β-carotene supplementation on the incidence of cardiovascular disease (29) or a slight increase in cardiovascular mortality (25, 27–29). However, only one of these trials was designed to address cardiovascular disease in particular (26). Several explanations have been proposed to explain the disparity between results obtained by observational and intervention studies. The duration and dosage of β-carotene may have been inadequate (30, 31) and β-carotene may have been administered too late in the carcinogenic or atherogenic process to be of benefit. (A protective effect of β-carotene may be most beneficial in the early phase of the carcinogenic or atherosclerotic process.) Adverse effects of supplemental β-carotene on plasma concentrations of other carotenoids have been reported (32, 33) and there is limited evidence that β-carotene could function as a prooxidant at higher concentrations (30). The associations found, however, cannot be ascribed to β-carotene exclusively. Possibly, β-carotene is a marker for some other substance in β-carotene–containing foods or for dietary patterns and lifestyle behavior closely linked to a diet rich in vegetables and fruit that is associated with reduced risk of ischemic heart disease. A habitual diet rich in β-carotene–containing products may thus also protect against ischemic heart disease in the elderly.

In the present study, we did not observe an association between dietary vitamin C and risk of MI. Our results agree with those of several other studies that did not find vitamin C to be associated with a protective effect against ischemic heart disease, as summarized by Jha et al (10). In studies in the elderly, some investigators observed an inverse association between cardiovascular diseases and high dietary vitamin C intakes and high plasma vitamin C concentrations (7), whereas others observed no association between cardiovascular diseases and high dietary vitamin C intakes and high plasma vitamin C concentrations (34) or use of vitamin C supplements (9). Results of a Finnish study linking vitamin C deficiency to an increased risk of MI (35) suggest that suboptimal vitamin C concentrations elevate the risk of MI. These findings are supported by experimental data showing that lipid peroxidation is detectable only after all ascorbate has been completely used up (36).

The most consistent, reliable, published beneficial effects of antioxidants on fatal and nonfatal cardiovascular diseases in middle-aged populations have been observed with vitamin E. These effects have been noted after both supplement use and relatively high dietary intakes (1, 4, 8, 37) sustained for ≥2 y (2, 3). The relative risk reduction for various cardiovascular endpoints ranged from 31% to 65% (10). In the present study, however, we

did not observe an association between dietary vitamin E intakes and reduced risk of MI. This finding is consistent with the findings of most studies that investigated the association between dietary vitamin E intakes and plasma vitamin E concentrations and risk of heart disease mortality in the elderly (7). Only one study observed an inverse association of vitamin E supplementation on ischemic heart disease risk in the elderly (9).

In summary, we found an inverse association between high dietary β-carotene intakes and risk of MI in an elderly population. Whether this association may be ascribed to β-carotene exclusively, to a diet rich in β-carotene–containing products, or to dietary patterns and lifestyle behavior closely linked to a diet rich in vegetables and fruit remains to be elucidated.

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